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Global Dynamics of TB Models with Density Dependent Demography

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Abstract

Mathematical models for Tuberculosis with linear and logistic growth rates are considered. The global dynamic structure for the logistic recruitment model is analyzed with the help of a strong version of the Poincaré-Bendixson Theorem. The nature of the global dynamics of the same model with a linear recruitment rate is established with the use of explicit threshold quantities controlling the absolute and relative spread of the disease and the likelihood of extinction or persistence of the total population. The classification of planar quadratic systems helps rule out the existence of closed orbits (limit cycles).

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1 Introduction

Tuberculosis (TB) was the main cause of death in many places around the world until the recent past. Although the situation has changed dramatically in the past century, TB still remains the main cause of death by an infectious (communicable) disease. Two million deaths per year are still attributed to TB.

Tuberculosis is an infectious disease with singular features, that is, its epidemiology is quite different from the epidemiology of most communicable diseases. TB's progression is quite slow and treatment (costly and relative difficult to implement) is available for the latent and active phases of the disease. TB, caused by *Mycobacterium tuberculosis*, responds to a complex treatment schedule and recovery or treatment do not give immunity. Lack of treatment can lead to death and resistance to antibiotics is a serious problem (Blower and Gerberding, 1998; Castillo-Chavez and Feng, 1997). The case fatality of untreated individuals is about 50% for pulmonary tuberculosis; a percentage that rises to about 75% when cases are also sputum positive (Styblo, 1991). Since the average rate of progression from infected (non-infectious) to active (infectious) TB is very slow, most (particularly in developing nations) infected individuals never develop active-TB. That is, the dynamics of TB at the population level are slow with characteristic time-scales of decades. Consequently, demography plays an important role on the transmission dynamics of TB and its partial assessment on TB is the main focus of this paper. We look at two distinct demographic scenarios: exponential growth on a long time scale and exponential growth on a short time scale (quasi-exponential growth). The effect of TB-induced mortality is considered on both demographic settings. Mathematical studies of the impact of fatal diseases on populations with demography have been carried out by many researchers (see Brauer, 1989; Busenburg and van den Driessche, 1990; Lin and Hethcote, 1993; Iannelli, Miller, and Pugliese, 1992; Brauer and Castillo-Chavez, 2001) but not in the context of tuberculosis(but see Aparicio *et al.*, 2001a and 2001b).

Quasi-exponential growth, a process that can be modeled and fitted to data using a linear demographic model with time-dependent per-capital growth rates, has been studied in the past (Cohen, 1995; Aparicio *et al.*, 2001a). For example, the USA population exhibited a quasi-exponential phase until the middle of the 18th century, a phase that has been followed by an almost linear growth phase afterwards. The pattern of USA population growth from Colonial Times to our days has been fitted to a logistic model (see for example, Aparicio *et al.*, 2001a). As Cohen (1995) points out most models used to fit demographic data can only give reasonable predictions over short periods of time at best. Many of the reasons behind the failure of demographic models in predicting patterns of population growth over long time scales are outlined in Cohen's recent book.

Many major cities in developed nations around the world that exhibited logistic growth had already reached (almost) stable values a few decades ago. The USA population growth pattern is different than those of developing nations (long-term quasi-exponential) or developed nations (no growth). The USA population is still growing albeit linearly. Hence, its growth is sort of intermediate between logistic and exponential. In this manuscript, we formulate a simple TB transmission model in a homogeneous population with demography. We show that demography does not impact the *qualitative* features of TB epidemics. That is, our results are qualitatively equivalent to those resulting from models for TB dynamics without demography (Blower *et al.*, 1995 and 1996; Castillo-Chavez and Feng, 1997 and 1998; Feng, Castillo-Chavez, and Huang, 2001). We establish the existence of a sharp "tipping point" with the help of natural non-dimensional thresholds that govern the transmission dynamics of TB and the nature of demographic growth.

The demographic setting is quite simple and well known (Brauer and Castillo-Chavez, 2001). We assume that the total population $N(t)$ is either governed by

$$\frac{dN}{dt} = (b - \mu)N, \tag{1}$$

where b is the per-capita birth rate and μ is per-capita mortality, both assumed constant (the total population N grows exponentially $N(t) = N_0 e^{rt}$ where $r = b - \mu$ is the net population growth rate and N_0 initial population size); or that $N(t)$ is modeled by

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right), \tag{2}$$

where K is the carrying capacity.

It is shown that the *qualitative* dynamics of TB are "essentially" the same when $N(t)$ is modeled by (1) or (2). In fact, the *qualitative* dynamics are identical to those without demography (Castillo-Chavez and Feng, 1997; Feng, Castillo-Chavez, and Huang, 2001). Our analysis is nevertheless useful as it identifies key thresholds in either case, that is, our analysis clarifies the role of demography. The global dynamic structure for the logistic recruitment model is studied with the help of a strong version of Poincaré-Bendixson Theorem while the nature of the global dynamics of the model with a linear recruitment rate is established with the use of explicit threshold quantities controlling the absolute and relative spread of the disease and the likelihood of extinction or persistence of the total population. The classification of planar quadratic systems is used to rule out the existence of closed orbits.

The rest of this paper is organized as follows: Section 2 introduces the epidemiological setting; Section 3 and 4 analyze the role of linear and logistic growth, respectively; Section 5 discusses the relevance of our results. Detailed analysis of the models, including the set up for the use of a strong version of the Poincaré-Bendixson Theorem, are included in the Appendix.

2 Epidemiological model

It is assumed that all immigrants and newborns are uninfected, that is, they are members of the susceptible class S. Infected individuals are divided into two classes: asymptomatic and non-infectious (latent-TB or inactive-TB), members of the class E; and symptomatic infectious (active-TB), members of the class I. Treated individuals are moved into the class T. Individuals in either the E-class or the I-class may enter the T-class by treatment or natural recovery.

Typically, latent individuals remain latent (in E-class) for a long period of time before progressing into the infectious class I, but progression is not uniform in general. Risk of progression to active-TB is higher soon after infection. Those who progress to active-TB within the first five years after infection are classified as *primary tuberculosis cases* while those who progress later are classified as *secondary tuberculosis cases.* Late progression (secondary cases) may be due to endogenous reactivation of the initial infection or *exogenous re-infection* (Styblo, 1991; Feng *et al.*, 2000). Infected individuals who do not progress to active-TB within the first years following primary infection are at a low risk of progression. There are many different ways of modeling this differential risk of progression (Blower *et al.*, 1995; Vynnycky and Fine, 1997; Aparicio *et al.*, 2000; Feng, Castillo-Chavez, and

Capurro, 2000; Thieme *et al.*, 1993; Feng, Castillo-Chavez, and Huang, 2001). The incorporation of primary tuberculosis and endogenous reactivation requires the introduction of age of infection(Vynnycky and Fine, 1997) but its incorporation adds complexity to the model. It may be reasonable to assume that, in the absence of re-infection, the distribution of new cases decays exponentially after the first infection (Styblo, 1991). In this manuscript, we ignore age-of-infection and assume a constant per-capita progression rate. The nature of this assumption limits the generality of our results for TB. The mathematical analysis of a general model with long and variable period of time in the E-class suggest that this assumption may not be as limited as it appears to be (Feng, Castillo-Chavez, and Huang, 2001).

Our simple transmission model, which preserves some of the main features of tuberculosis epidemiology, is given by

$$\frac{dS}{dt} = B(N) - \beta c S \frac{I}{N} - \mu S, \tag{3}$$

$$\frac{dE}{dt} = \beta c S \frac{I}{N} - (\mu + k + \alpha)E + \beta' c T \frac{I}{N}, \tag{4}$$

$$\frac{dI}{dt} = kE - (\mu + d + \rho)I, \tag{5}$$

$$\frac{dT}{dt} = \alpha E + \rho I - \beta' c T \frac{I}{N} - \mu T, \tag{6}$$

$$N = S + E + I + T,$$

where the recruitment rate $B(N)$ is either bN or $b_0 N(1 - \frac{N}{K})$. [The form $B(N) = \Lambda - \mu N$ was also used by Castillo-Chavez and Feng (1997 and 1998).] We let β and β' denote the average infected proportions of susceptible and treated individual contacted by one infectious individual per unit of time, respectively; c is the per-capita contact rate; $\beta c S \frac{I}{N}$ and $\beta' c T \frac{I}{N}$ denote the infection and reinfection rates, respectively; μ denotes the per-capita mortality rate; d the TB-induced mortality rate; k the per-capita rate of progression to active-TB from latent-TB(class E); α and ρ denote the treatment rates for the latent and infectious class, respectively.

Because TB increases mortality, both demography and epidemiology are incorporated into the equation that governs the dynamics of the total population, that is, we have that

$$\frac{dN}{dt} = B(N) - \mu N - dI \tag{7}$$

Currently, most deaths caused by TB represent but a small proportion of the deaths in most populations. In other words, d is often insignificant. Therefore, a linear recruitment rate $B(N) = b_0 N$ with reasonable b_0 values is likely to support exponential growth on a TB-infected population. The use of a logistic recruitment rate $B(N) = b_0 N(1 - \frac{N}{K})$ to model the demography in general is also likely to result in logistic growth for the total population N in the presence of TB.

To simplify our analysis, we further assume that infected and reinfected proportions are equal, $\beta' = \beta$. Hence, the use of the variables, N, E and I, is now enough, that is, Model(??-??) reduces to:

$$\frac{dN}{dt} = B(N) - \mu N - dI, \tag{8}$$

$$\frac{dE}{dt} = \beta c(N - E - I)\frac{I}{N} - (\mu + k + \alpha)E, \tag{9}$$

$$\frac{dI}{dt} = kE - (\mu + d + \rho)I. \tag{10}$$

Throughout this paper, we shall consistently use the following compressed notations $m_r = b_0 + \rho + d, n_r = b_0 + \alpha + k, m_\mu = \mu + \rho + d, n_\mu = \mu + \alpha + k$, and $\sigma = \beta c$ to simplify the discussions.

3 Linear recruitment rate

In this section, we study the dynamics of Model (??-??) with $B(N) = b_0 N$. That is, it is assumed that the total population exhibits exponential growth in the absence of TB (the net growth rate of the population, in the absence of the disease, is $r \equiv b_0 - \mu$). Total population size increases (decreases) exponentially if $b_0 > \mu$ ($b_0 < \mu$), and remains constant if $b_0 = \mu$. The case where $b_0 < \mu$ is trivial. Hence we assume that $b_0 \geq \mu$. In the presence of TB the total population may (theoretically) decrease exponentially even when $b_0 > \mu$ provided that d is large enough. That is, technically, a fatal disease like TB can control population growth (see also May and Anderson, 1985). Realistic examples of situations where a disease has impacted or is likely to impact demographic growth can be found in the work on myxomatosis by Levin and Pimentel (1981) or in the work on HIV by Anderson, May, and Mclean (1988 and 1989).

Three non-dimensional threshold parameters provide a full characterization of the possible dynamical regimes of System (??-??): $\mathcal{R}_0$, $\mathcal{R}_1$ and $\mathcal{R}_2$.

The basic reproductive number given by

$$\mathcal{R}_0 = \left(\frac{\sigma}{\mu+\rho+d}\right)\left(\frac{k}{\mu+\alpha+k}\right), \tag{11}$$

gives the average number of secondary cases produced by a typical infectious individual during his/her entire life in a population of mostly susceptibles. $\mathcal{R}_0 < 1$ implies that the infected populations goes to zero while $\mathcal{R}_0 > 1$ implies that the infected populations grows (initially) exponentially (together with the total population N). In this last case there are two possibilities: N grows faster than I or N does not grow faster than I. In the first case, the fraction $u = \frac{I}{N}$ approaches zero as time increases and the additional threshold parameter

$$\mathcal{R}_1 = \left(\frac{\sigma}{b_0+\rho+d}\right)\left(\frac{k}{b_0+\alpha+k}\right) \tag{12}$$

plays a role. $\mathcal{R}_1$ discriminates between the last two possibilities. $\mathcal{R}_1 < 1$ implies that $\lim_{t\to\infty} u = 0$ while $\mathcal{R}_1 > 1$ implies that $\lim_{t\to\infty} u = u^*$ where u^* is a positive constant. Because by assumption $b_0 > \mu$, we always have that $\mathcal{R}_0 > \mathcal{R}_1$.

If the infectious (I) population changes faster than the total population (N) then a fatal disease can drive the population to extinction (even when $\mathcal{R}_1 > 1$). The threshold parameter that decides this last situation is given by

$$\mathcal{R}_2 = \frac{b_0-\mu}{du^*}, \tag{13}$$

where u^* is a positive constant (independent of μ (see (??)), that is, $\mathcal{R}_2$ determines whether or not the total population size grows exponentially. It will be shown later that the population size decreases exponentially (because of TB) only if $\mathcal{R}_2 < 1$.

A detailed characterization of the dynamics of System (??-??) is provided in the rest of this section with the mathematical details included in the appendix.

System (??-??) is homogeneous of degree one and, hence, it can support exponential solutions. Hadeler's theory for the study of the linear (local) stability of homogeneous systems (Hadeler, 1990 and 1992) applies albeit it does not address the issue of the global stability of solutions, the main focus of our analysis. Global analysis requires the rewriting of System (??-??) using the projections $u = \frac{I}{N}$, and $v = \frac{E}{N}$. The equations for u, v are given by the following quadratic system:

$$\frac{du}{dt} = -m_r u + kv + du^2, \tag{14}$$

$$\frac{dv}{dt} = \sigma u - n_r v + (d-\sigma)uv - \sigma u^2. \tag{15}$$

Note that both u and v are independent of N and μ. It is easy to check that the subset

$$\Omega = \{(u,v) \in \mathbf{R}_2^+ | u + v \leq 1\}$$

is positively invariant. To further simplify the quadratic System (??-??), we introduce the new variables x and y and rescale time t. Specifically, we let

$$x = \frac{d}{m_r + n_r} u, \quad y = \frac{kd}{(m_r+n_r)^2}\left(\frac{n_r}{k}u + v\right), \quad and \quad \tau = (m_r + n_r)t. \tag{16}$$

The re-scaled system becomes

$$\frac{dx}{d\tau} = -x + y + x^2, \tag{17}$$

$$\frac{dy}{d\tau} = x(a_1 + a_2 y + a_3 x), \tag{18}$$

where

$$a_1 = \frac{m_r n_r(\mathcal{R}_1 - 1)}{(m_r+n_r)^2}, \quad a_2 = \frac{d-\sigma}{d}, \quad and \quad a_3 = \sigma\frac{n_r - k}{d(m_r+n_r)}.$$

In the new system, Ω becomes

$$\Omega_1 = \left\{(x,y) \in \mathbf{R}_2^+ | \frac{n_r}{m_r+n_r}x \leq y \leq \frac{dk}{(m_r+n_r)^2} + \frac{n_r - k}{m_r+n_r}x\right\}$$

which is positively invariant under the flow of System (??-??). This last transformation not only reduces the number of parameters but, more importantly, it fixes the horizontal isocline and decomposes the vertical isocline into a degenerate quadratic curve. Under the standard classification of Ye *et al.*. (1986), System (??-??) is *a quadratic system of the second type.*

The following two theorems characterize the dynamics of System (??-??) and hence of (??-??). Proofs are in the Appendix.

Theorem 1. *For System (??-??) with* $b_0 > \mu$, *the trivial equilibrium* $(0,0)$ *is globally asymptotically stable if* $\mathcal{R}_1 \leq 1$. *Furthermore there exists a unique positive equilibrium which is globally asymptotically stable if* $\mathcal{R}_1 > 1$.

The standard classification of planar quadratic differential systems rules out the existence of closed orbits or limit cycles. (Other approaches can be used to draw the same conclusion, for example, see Busenberg and van den Driessche, 1990; Lin and Hethcote, 1993). The full structure of the System (??-??) is characterized in Theorem ?? below:

Theorem 2. *Consider System (??-??) and assume that* $b_0 > \mu$.

(a) If $\mathcal{R}_0 < 1$ *then* $(\infty, 0, 0)$ *is globally asymptotically stable.*

(b) If $\mathcal{R}_1 < 1 < \mathcal{R}_0$ *then* (∞, ∞, ∞) *is globally asymptotically stable and* $\lim\limits_{t\to\infty} \frac{I}{N} = 0$, $\lim\limits_{t\to\infty} \frac{E}{N} = 0$.

(c) If $1 < \mathcal{R}_1 < \mathcal{R}_0$ *then*

i) $(0,0,0)$ *is globally asymptotically stable and* $\lim\limits_{t\to\infty} \frac{I}{N} = u^*$, $\lim\limits_{t\to\infty} \frac{E}{N} = v^*$ *when* $\mathcal{R}_2 < 1$,

ii) (∞, ∞, ∞) *is globally asymptotically stable and* $\lim\limits_{t\to\infty} \frac{I}{N} = u^*$, $\lim\limits_{t\to\infty} \frac{E}{N} = v^*$ *when* $\mathcal{R}_2 > 1$, *where*

$$
\begin{aligned}
u^* &= \frac{-[d(m_r + n_r) - \sigma(m_r + k)] + \sqrt{\delta}}{2d(\sigma - d)(k\sigma - m_r n_r)}, \qquad (19)\\
v^* &= \frac{m_r(a_2 + a_3 + \Delta^{1/2}) - 2a_2 d u^{*2}}{2a_2 k},\\
\delta &= [d(m_r + n_r) - \sigma(m_r + k)]^2 + 4d(\sigma - d)(k\sigma - m_r n_r),\\
\Delta &= (a_2 + a_3)^2 + 4a_1 a_2 > 0.
\end{aligned}
$$

Hence, whenever $\mathcal{R}_0 < 1$ the disease dies out while the total population increases exponentially. Although the disease spreads when $\mathcal{R}_1 < 1 < \mathcal{R}_0$, the proportions $\frac{I}{N}$ and $\frac{E}{N}$ approach zero. From (c) one sees that disease-induced mortality can lead to the extinction of a population which would otherwise increase exponentially (a fatal disease can regulate a population). Note that $\mathcal{R}_2$ is a positive number since u^* is positive and independent of μ. We have also established that when $b_0 < \mu$, $(0,0,0)$ is globally asymptotically stable even though $\lim_{t\to\infty} \frac{I}{N} = u^*$ and $\lim_{t\to\infty} \frac{E}{N} = v^*$ when $\mathcal{R}_1 > 1$. $\mathcal{R}_1 < 1$ implies that $\lim_{t\to\infty} \frac{I}{N} = 0, \lim_{t\to\infty} \frac{E}{N} = 0$. Note that $\mathcal{R}_1 < \mathcal{R}_0$ whenever $b_0 > \mu$. Theorem ?? provides a complete characterization of the dynamic structure of Model (??-??).

4 Logistic recruitment rate

In this section, we study the case where $B(N) = b_0N(1 - \frac{N}{K})$. Since the total population N is now bounded, a threshold parameter like $\mathcal{R}_1$, which determines the asymptotic behavior of the proportions, is meaningless in this setting.

Re-scaling N by $\frac{N}{K}$, I by $\frac{I}{K}$ and E by $\frac{E}{K}$ reduces Model (??-??) to

$$\frac{dN}{dt} = b_0N(1-N) - \mu N - dI, \tag{20}$$

$$\frac{dE}{dt} = \beta c(N - E - I)\frac{I}{N} - (\mu + k + \alpha)E, \tag{21}$$

$$\frac{dI}{dt} = kE - (\mu + d + \rho)I. \tag{22}$$

The dynamics of this model are characterized by the following theorem:

Theorem 3. *For System (??-??), if $\mathcal{R}_0 \leq 1$, the disease-free equilibrium is globally asymptotically stable; while if $\mathcal{R}_0 > 1$ and $\mathcal{R}_2^* > 1$, there exists a unique endemic equilibrium point where*

$$\mathcal{R}_2^* = \frac{b_0}{\mu + d\frac{k}{\mu+d+\rho+k}\frac{\mathcal{R}_0 - 1}{\mathcal{R}_0}}. \tag{23}$$

Remark. In the proof (see the Appendix), we show that the disease not only dies out when the basic reproductive is less than or equal to one, but also that it dies out *exponentially fast* (see Equation (??) with an exponential rate of decay of the order of $1 - \mathcal{R}_0$. The approach followed in Thieme (1993) can be used to show that the disease-free equilibrium is globally asymptotically stable; however, no result about the rate of convergence can be derived from this approach. The global stability of the trivial equilibrium is also established when $\mathcal{R}_0 = 1$.

In order to show that the endemic equilibrium is globally asymptotically stable, we need to assume that $b_0 > \mu + 2d\sigma(\sigma + \alpha - \rho - d)$. This assumption does not conflict with the assumption that $\mathcal{R}_0 > 1$ since $\mathcal{R}_0$ does not depend on b_0 at all. We collect the results in our last theorem:

Theorem 4. *For System (??-??), if $\mathcal{R}_0 > 1$ and $\mathcal{R}_2^* > 1$, then the endemic equilibrium is globally asymptotically stable, provided that $\alpha > d$ and $b_0 > \mu + 2d\sigma(\sigma + \alpha - \rho - d)$.*

5 Discussion and conclusions

Slow progression rates from the latently-infected to the infectious stage are characteristic of tuberculosis, a disease with slow dynamics. A growing infected population may go hand in hand with a decreasing infected fraction (prevalence) whenever the population growth rate is greater than that of its infected subpopulation. In this last case, TB is not being eradicated but "diluted" by the populations fast demographic growth. When the total population is bounded, our model predicts stable levels for the infected populations (given that $\mathcal{R}_0 > 1$). These constant levels are reached in a (quasi) monotonous way. This qualitative prediction is corroborated by epidemiological records. Damped oscillations or limit cycles are not found on TB data. However, there is still a need for more detailed models as shifts in epidemiological parameter values or the emergence of new diseases (like AIDS) can change, at least temporarily, the transmission dynamics of TB. Landscape changes may produce (sometimes dramatic) changes on the *quantitative* features of TB dynamics (Aparicio *et al.*, 2001a).

Reliable records associated with tuberculosis mortality go back two hundred years in many developed countries. From these records one can see that TB was not able to generate negative population growth rates in spite of the fact that tuberculosis was, in many places, the main cause of death. Its "limited" demographic impact may have been, in part, the result of (relatively) slow progression rates from the latent to the active (and often fatal) state. This is not surprising. The world population has experienced continuous steady (in most places) growth despite the impact of fatal diseases like tuberculosis and wars (Cohen, 1995). Most population growth patterns in the past have been quasi-exponential despite disease, famine, and wars. Hence, our analysis of the impact of TB on populations exhibiting exponential or quasi-exponential (logistic) growth covers most observed population growth patterns. Our results show that TB generates long-term and often short-term "boring" disease patterns. Furthermore, population growth combined with strong declines on TB progression rates (Aparicio *et al.*, 2001a) can explain the (often dramatic) quantitative changes observed on TB dynamics. Changes have had no impact on TB's long-term *qualitative* features but strong impact on its *quantitative* dynamics. The study of the evolutionary dynamics of slow progressing diseases like TB must therefore include demography and more. Host heterogeneity, geography and social structure are some of the critical factors needed in the study of the evolution of slow diseases like TB. We hope to incorporate some form of host heterogeneity in order to take on some of these challenges.

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A Appendix

A.1 Proof of Theorem ??

Proof. The proof is divided into three parts. First, we prove that the trivial equilibrium $A_0(0,0)$ of System (??-??) is globally asymptotically stable if $\mathcal{R}_1 < 1$. Then, it is proved that if $\mathcal{R}_1 > 1$ $A_0(0,0)$ is unstable and a unique positive equilibrium is born. Finally, we show that this positive equilibrium is globally asymptotically stable whenever it exists.

Part 1. If $\mathcal{R}_1 < 1$, $A_0(0,0)$ is the trivial equilibrium of System (??-??) and it is locally asymptotically stable. To show that A_0 is the unique positive equilibrium on Ω_1 we proceed as follows: Ω_1 is a triangle surrounded by $x=0$, $y=\frac{n_r}{m_r+n_r}x$ and $y=\frac{kd}{(m_r+n_r)^2}+\frac{n_r-k}{m_r+n_r}x$. The equilibria of System (??-??) live at the intersections of the straight line $a_1+a_2y+a_3x=0$ and the parabola $y=x-x^2$. After some tedious algebraic calculations, we find out that this straight line is outside Ω_1, whenever $\mathcal{R}_1 < 1$; that is, the trivial equilibrium is unique, whenever $\mathcal{R}_1 < 1$. Because $A_0(0,0)$ is located on the boundary of the positive invariant subset Ω_1, there is no closed orbit around it. Thus, $A_0(0,0)$ is globally asymptotically stable.

Part 2. $\mathcal{R}_1 > 1$ implies $|J_{A_0}| < 0$ and thus A_0 is a saddle. Let $A_1(x^*,y^*)$ be an equilibrium of (??-??) in Ω_1. x^* of (??-??) must be a positive solution of the quadratic equation $f(x)=x-x^2+\frac{a_3}{a_2}x+\frac{a_1}{a_2}=0$. If we let $x_{2,4}=\frac{m_rn_r(1-\mathcal{R}_1)d}{(m_r+n_r)(dn_r-k\sigma)}$ and $x_{3,2}=\frac{d}{m_r+n_r}$ then $f(x)=0$ will have a unique root in the interval $[0,\frac{d}{m_r+n_r}]$. In fact, if $\mathcal{R}_1 > 1$, then $0 < x_{2,4} < x_{3,2}$, and $\sigma > r+\rho+d > d$. Hence,

$$f(0)=\frac{a_1}{a_2}=\frac{m_rn_r(\mathcal{R}_1-1)d}{(m_r+n_r)^2(d-\sigma)}<0,$$

$$f(x_{2,4})=x_{2,4}\big(\frac{m_r}{m_r+n_r}-x_{2,4}\big)>x_{2,4}\big(\frac{m_r}{m_r+n_r}-x_{3,2}\big)=x_{2,4}\frac{r+\rho}{m_r+n_r}>0,$$

and $f(+\infty)=-\infty$. Therefore, one solution of $f(x)=0$ is in $[0,\frac{d}{m_r+n_r}]$, and the other is in $[\frac{d}{m_r+n_r},+\infty)$, located outside of Ω_1. Explicitly, $A_1(x^*,y^*)=\Big(\frac{a_2+a_3+\Delta^{\frac{1}{2}}}{2a_2},x^*(1-x^*)\Big)$ where $\Delta=(a_2+a_3)^2+4a_1a_2>0$.

Part 3. We prove $A_1(x^*, y^*)$ is globally asymptotically stable.

$$J_{A_1} = \begin{pmatrix} 2x^* - 1 & 1 \\ a_3 x^* & a_2 x^* \end{pmatrix}$$

is the Jacobian matrix of System (??-??) evaluated at $A_1(x^*, y^*)$. $|J_{A_1}| = x^*(2a_2 x^* - a_2 - a_3) = x^* \Delta^{\frac{1}{2}} > 0$ and $-tr(J_{A_1}) = 1 - 2x^* - a_2 x^* = \frac{a_3 + \Delta^{\frac{1}{2}}}{-a_2} - a_2 x^* > 0$, where the last inequality was derived from that fact that $a_2 < 0$ (which is implied by $\mathcal{R}_1 > 1$). A_1 is thus a locally asymptotically stable equilibrium. Moreover it is a node, since

$$[-tr(J_{A_1})]^2 - 4|J_{A_1}| = [1 - (2 + a_2)x^*]^2 - 4x^* \Delta^{\frac{1}{2}} = \left(\frac{\Delta^{\frac{1}{2}}}{a_2} - a_2 x^* \right)^2 \geq 0.$$

Consequently, System (??-??) is a quadratic differential system of type two. It follows from Ye (1986) that there are no closed orbits around A_1. Hence, A_1 is globally asymptotically stable. □

A.2 Proof of Theorem ??

Proof. $\Omega_0 = \{(N, E, I) \in R_3^+ | E + I \leq N\}$ is a positive invariant subset of System (??-??). Part (a) of Theorem ?? is a particular case of Theorem ?? since $\mathcal{R}_1 < \mathcal{R}_0$. Thus we only need to prove part (b) and part (c). If $\mathcal{R}_1 < 1$ (from Theorem ??) then $\lim_{t\to\infty} \frac{I}{N} = 0$ and $\lim_{t\to\infty} \frac{E}{N} = 0$. Equation (??) can be rewritten as

$$\frac{1}{N}\frac{dN}{dt} = (b_0 - \mu) - d\frac{I}{N},$$

from which it follows that $\lim_{t\to\infty} N(t) = +\infty$. Hence, we only need to show that

$$\lim_{t\to\infty} I(t) = \lim_{t\to\infty} E(t) = +\infty.$$

Solving Equation (??) formally one sees that

$$E(t) = \frac{E_0 + \int_0^t \left(\sigma I(1 - \frac{I}{N}) exp(n_\mu \zeta + \int_0^\zeta \sigma \frac{I}{N} ds)\right) d\zeta}{exp(n_\mu t + \int_0^t \sigma \frac{I}{N} ds)}.$$

L'Hospital's rule (limit inferior) gives

$$E_\infty = \liminf_{t\to\infty} E(t) \geq \liminf_{t\to\infty} \left(\frac{\sigma}{n_\mu + \sigma \frac{I}{N}} I(1 + \frac{I}{N}) \right) = \sigma \frac{I_\infty}{n_\mu}. \qquad (24)$$

Similarly, one establishes that

$$I_\infty \geq \frac{kE_\infty}{m_\mu}. \tag{25}$$

Combining (??) and (??) yields

$$\frac{\sigma I_\infty}{n_\mu} \leq E_\infty \leq \frac{m_\mu I_\infty}{k}. \tag{26}$$

From (??) it follows that $I_\infty = 0$ if and only if $E_\infty = 0$. It also follows that $I_\infty = +\infty$ if and only if $E_\infty = +\infty$. To show $I_\infty > 0$ we analyze the trajectories of System (??-??). Evaluating $\frac{dE}{dt}$ along $kE - m_\mu I = 0$ gives

$$\frac{dE}{dt}\Big|_{kE-m_\mu I=0} = I\left(\sigma - \frac{n_\mu m_\mu}{k} - \sigma\left(\frac{I}{N} + \frac{E}{N}\right)\right).$$

If a trajectory $(N(t), E(t), I(t))$ intersects the plane $kE - m_\mu I = 0$ (when time t is sufficiently large) then $\frac{dE}{dt}|_{kE-m_\mu I=0} > 0$. This last remark is true because $\lim_{t\to\infty} \frac{I}{N} = 0$, $\lim_{t\to\infty} \frac{E}{N} = 0$ and $\mathcal{R}_0 > 1$. That is, whenever $t >> 1$, the trajectories cannot leave the set Ω_0 - $\bar{\Omega}_0$, where $\bar{\Omega}_0 = \{(N, E, I) \in R_3^+ | kE > m_\mu I\} \cap \Omega_0$, that is, they must remain either in $\bar{\Omega}_0$ or in $\Omega_0 - \bar{\Omega}_0$. If the former is true then $\frac{dI}{dt} > 0$ which gives $I_\infty > 0$. If the latter is true then

$$\frac{dE}{dt} \geq I\left[(\sigma - \frac{m_\mu n_\mu}{k}) - \sigma(\frac{I}{N} + \frac{E}{N})\right] \geq 0$$

which yields $E_\infty > 0$ and $I_\infty > 0$. However, according to (??), if $I_\infty < +\infty$ then

$$0 < I_\infty \frac{(k\sigma - m_\mu n_\mu)}{kn_\mu} \leq 0,$$

which contradicts the fact that $I_\infty = E_\infty = +\infty$.

The proof of (c) is shorter. According to Theorem ??, $\mathcal{R}_1 > 1$ leads to $\lim_{t\to\infty} \frac{I}{N} = u^*$. The limiting equation of Equation (??) is

$$\frac{dN}{dt} = Ndu^*(\mathcal{R}_2 - 1). \tag{27}$$

It follows from the theory of limiting equations (Thieme, 1992 and 1994; Thieme and Castillo-Chavez, 1995) that $N(t)$ is asymptotically equal to $e^{du^*(\mathcal{R}_2-1)t}$ by which (c) is established and the proof is complete. $\square$

A.3 Proof of Theorem ??.

Proof. The disease-free equilibrium is $(\frac{b_0-\mu}{b_0}, 0, 0)$. It is straightforward to show that the endemic equilibrium is unique whenever $\mathcal{R}_0 > 1$ and $\mathcal{R}_2^* > 1$ and the disease-free equilibrium is locally stable whenever $\mathcal{R}_0 \leq 1$. Here, we only need to establish the global stability of the disease-free equilibrium under the assumption $\mathcal{R}_0 \leq 1$.

Let

$$f(t) = \gamma E(t) + 2\sigma I(t), \quad \text{where} \quad \gamma = \sqrt{(m_\mu - n_\mu)^2 + 4k\sigma} + m_\mu - n_\mu.$$

It suffices to show $\lim_{t\to\infty} f(t) = 0$.

$$\begin{aligned}
\frac{df(t)}{dt} &= \gamma\frac{dE(t)}{dt} + 2\sigma\frac{dI(t)}{dt} \\
&\leq \gamma(\sigma I(t) - n_\mu E(t)) + 2\sigma(kE(t) - m_\mu I(t)) \\
&= (2\sigma k - \gamma n_\mu)E(t) + (\gamma\sigma - 2\sigma m_\mu)I(t) \\
&= (-n_\mu + \frac{2\sigma k}{\gamma})\gamma E(t) + (\frac{\gamma}{2} - m_\mu)2\sigma I(t) \\
&= (\gamma E(t) + 2\sigma I(t))\left(\frac{\sqrt{(m_\mu - n_\mu)^2 + 4\sigma k} - (m_\mu + n_\mu)}{2}\right) \\
&= -\frac{(1 - \mathcal{R}_0)}{\sqrt{(m_\mu - n_\mu)^2 + 4\sigma k} + m_\mu + n_\mu} f(t).
\end{aligned}$$

This actually produces a differential inequality on the function $f(t)$, that is,

$$\frac{df(t)}{dt} < -\frac{(1 - \mathcal{R}_0)}{\sqrt{(m_\mu - n_\mu)^2 + 4\sigma k} + m_\mu + n_\mu} f(t). \tag{28}$$

It follows that $\lim_{t\to\infty} f(t) = 0$ from the fact that $\frac{(1-\mathcal{R}_0)}{\sqrt{(m_\mu - n_\mu)^2 + 4\sigma k + m_\mu + n_\mu}} > 0$ when $\mathcal{R}_0 < 1$.

If $\mathcal{R}_0 = 1$, $f(t)$ no longer decays exponentially, but it still vanishes as time goes to infinite. We estimate the derivative of $f(t)$ again.

$$\begin{aligned}
\frac{df(t)}{dt} &= -\sigma\gamma(E + I)\frac{I}{N} \\
&\leq -\sigma\gamma(E + I)I \\
&\leq -\gamma_1 I f(t), \quad \text{where} \quad \gamma_1 = \frac{min\{2\sigma, \gamma\}}{2} > 0.
\end{aligned}$$

This gives that $f(t)$ is decreasing and that

$$f(t) \leq f(0)e^{-\gamma_1 \int_0^t I(t)dt}. \tag{29}$$

If $\liminf_{t\to\infty} I(t) > 0$ then $\lim_{t\to\infty} f(t) = 0$ by (??) which yields $\lim_{t\to\infty} I(t) = 0$ from the definition of $f(t)$. Hence, $\liminf_{t\to\infty} I(t) = 0$. It follows that $\liminf_{t\to\infty} E(t) = 0$ from the fluctuation lemma of Hirsch, Hanisch, and Gabriel (1985) and Proposition 2.2 by Thieme (1993). Consequently, $\liminf_{t\to\infty} f(t) = 0$ and $\lim_{t\to\infty} f(t) = 0$ because $f(t)$ is decreasing. □

A.4 Proof of Theorem ??.

The proof of the Theorem ?? is a consequence of four lemmas. Introducing a new variable $Y = E + I$, we arrive at an equivalent system to (??-??)

$$\frac{dN}{dt} = b_0 N(1-N) - \mu N - dI, \tag{30}$$

$$\frac{dY}{dt} = \sigma(N-Y)\frac{I}{N} - (\mu+\alpha)Y + (\alpha - \rho - d)I, \tag{31}$$

$$\frac{dI}{dt} = kY - (\mu + d + \rho + k)I. \tag{32}$$

Lemma 1. *Let $N(t)$, $Y(t)$ and $I(t)$ be the solution of System (??-??). If $\alpha \geq d$, then*

$$\liminf_{t\to\infty}\left(\alpha - \rho - d + \sigma\frac{N(t) - Y(t)}{N(t)}\right) > 0.$$

Proof. Directly examine the long-term behavior of the function

$$f(t) = \alpha - \rho - d + \sigma\frac{N(t)-Y(t)}{N(t)} = \alpha - \rho - d + \sigma - \sigma\frac{Y(t)}{N(t)}.$$

By differentiation,

$$\begin{aligned}
\frac{df}{dt} &= -\sigma \frac{\frac{dY}{dt}N - \frac{dN}{dt}Y}{N^2} \\
&= -\sigma\left(\frac{\sigma(N-Y)}{N}\frac{I}{N} - (\mu+\alpha)\frac{Y}{N} + (\alpha-\rho-d)\frac{I}{N} - \frac{Y}{N}(b_{)}(1-N) - \mu - d\frac{I}{N})\right) \\
&= -\sigma\frac{I}{N}\left(\sigma\frac{(N-Y)}{N} + \alpha - \rho - d\right) + \sigma\frac{Y}{N}\left(\alpha + b_0(1-N) - d\frac{I}{N}\right) \\
&\geq -\sigma\frac{I}{N}f(t) + \sigma\frac{Y}{N}\left(\alpha - d + b_0(1-N)\right) \quad (\frac{I}{N} \leq 1) \\
&\geq -\sigma\frac{I}{N}f(t), \quad (\alpha > d \text{ and } 1 > N)
\end{aligned}$$

from which we obtain

$$f(t) \geq f(t_0)e^{-\sigma\int_{t_0}^{t}\frac{I(s)}{N(s)}ds} \geq f(t_0)e^{-\sigma(t-t_0)}.$$

Hence,

$$\liminf_{t\to\infty} f(t) \geq \liminf_{t\to\infty}\left(f(t_0)e^{-\sigma\int_{t_0}^{t}\frac{I(s)}{N(s)}ds}\right) = 0.$$

□

Remark. Using Lemma 1, it can be verified that any trajectory of System (??-??) will eventually enter the region

$$V = \left\{(N,Y,I) \in R_+^3, 1 \geq N \geq Y \geq I, \alpha - \rho - d + \sigma \geq \sigma\frac{Y}{N}\right\}.$$

In fact, V is positive invariant on orbits in System (??-??).

Lemma 2. *Under the assumptions of Theorem ??, if $N(t)$ is a periodic solution, then $b_0 - \mu - 2b_0N(t) < 0$*

Proof. From Lemma ??

$$\sigma\frac{Y}{N} \leq \sigma + \alpha - \rho - d\sigma$$

gives

$$I \leq Y \leq \frac{N}{\sigma}(\sigma + \alpha - \rho - d).$$

Consequently,

$$\frac{dN}{dt} \geq b_0N(1-N) - \mu N - \frac{d}{\sigma}(\sigma+\alpha-\rho-d)N$$
$$= (b_0 - \mu - \frac{d}{\sigma}(\sigma+\alpha-\rho-d))N - b_0N^2.$$

It follows from the comparison principle that

$$N(t) \geq \frac{1}{b_0}(b_0 - \mu - \frac{d}{\sigma}(\sigma+\alpha-\rho-d)) \text{ whenever t is large enough,}$$

which holds for all t because $N(t)$ is periodic (by assumption). Finally,

$$b_0-\mu-2b_0N \leq b_0-\mu-2((b_0-\mu-\frac{d}{\sigma}(\sigma+\alpha-\rho-d)) = -b_0+\mu+\frac{2d}{\sigma}(\sigma+\alpha-\rho-d) < 0.$$

Hence Lemma ?? is true. □

Lemma 3. *System (??-??) is equivalent to a monotone system in the region V.*

The proof of Lemma ?? can be done by choosing

$$\mathcal{E} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

and verifying that $\mathcal{E}^{-1}J\mathcal{E}$ is a non-positive matrix, where J is the Jacobian matrix of the System (??-??), that is,

$$J = \begin{pmatrix} b_0 - \mu - 2b_0N & 0 & -d \\ \frac{\sigma IY}{N^2} & -(\alpha+\mu+\frac{\sigma I}{N}) & \alpha+\sigma\frac{N-Y}{N}-\rho-d \\ 0 & k & -(\rho+d+\mu+k) \end{pmatrix}.$$

Lemma 4. *Under the assumptions of Theorem ??, any periodic solution of (??-??) is stable, if it exists.*

Proof. $J^{[2]}$ is the compound matrix of J. By the Theorem 4.2 in Muldowney (1990), it is enough to show the linear system

$$\frac{dX}{dt} = J^{[2]}X \tag{33}$$

with

$$J^{[2]} = \begin{pmatrix} b_0 - \mu - 2b_0N - \alpha - \sigma\frac{I}{N} & \alpha + \sigma\frac{I}{N} & d \\ k & b_0 - 2\mu - 2N - d - \rho - k & 0 \\ 0 & \sigma\frac{IY}{N^2} & -(m_\mu + n_\mu + \sigma\frac{I}{N}) \end{pmatrix}$$

is asymptotically stable. To establish this result, we write (??) explicitly, that is,

$$\begin{aligned}
\frac{dx_1}{dt} &= \left(b_0 - \mu - 2b_0N(t) - \alpha - \sigma\frac{I(t)}{N(t)}\right)x_1 + \left(\alpha + \sigma\frac{N(t) - Y(t)}{N(t)}\right)x_2 + dx_3, \\
\frac{dx_2}{dt} &= kx_1 + \left(b_0 - \mu - 2b_0N(t) - d - \rho - k\right)x_2, \\
\frac{dx_3}{dt} &= \sigma\frac{I(t)Y(t)}{N(t)^2}x_2 - \left(m_\mu + n_\mu + \sigma\frac{I(t)}{N(t)}\right)x_3.
\end{aligned}$$

Define $D_+x(t)$ to be the right upper derivative of $x(t)$ with respect to t, i.e.,

$$D_+x(t) = \limsup_{\Delta t \to 0^+} \frac{x(t+\Delta t) - x(t)}{\Delta t}.$$

Applying the operator D_+ to each $|x_i(t)|$, we derive the following inequalities:

$$\begin{aligned}
D_+|x_1(t)| \le& \left(b_0 - \mu - 2b_0N(t) - \alpha - \sigma\frac{I(t)}{N(t)}\right)|x_1(t)| \\
&+ \left(\alpha + \sigma\frac{N(t) - Y(t)}{N(t)}\right)|x_2(t)| + d|x_3(t)|, \\
D_+|x_2(t)| \le& k|x_1(t)| + \left(b_0 - \mu - 2b_0N(t) - d - \rho - k\right)|x_2(t)|, \\
D_+|x_3(t)| \le& \sigma\frac{I(t)Y(t)}{N(t)^2}|x_2(t)| - \left(m_\mu + n_\mu + \sigma\frac{I(t)}{N(t)}\right)|x_3(t)|.
\end{aligned}$$

To show that $\lim_{t\to\infty} x_i(t) = 0$ holds simultaneously for $i = 1, 2, 3$, define

$$Q(t) = max\left\{|x_1(t)|, \frac{Y(t)}{I(t)}|x_2(t)|, \frac{N(t)}{I(t)}|x_3(t)|\right\}.$$

At any t, $Q(t)$ takes three possible values, $|x_1(t)|$, $\frac{Y(t)}{I(t)}|x_2(t)|$, and $\frac{N(t)}{I(t)}|x_3(t)|$. If

$Q(t) = |x_1(t)|,$

$$\begin{aligned}
D_+Q(t) &= D_+|x_1(t)| \\
&\leq \left(b_0 - \mu - 2b_0N - \alpha - \sigma\frac{I}{N} + (\alpha - \rho - d + \sigma\frac{N-Y}{N})\frac{I}{Y} + d\frac{I}{N}\right)|x_1(t)| \\
&\leq Q\left(b_0 - \mu - 2b_0N - d\frac{I}{N} + (\alpha - \rho - d + \sigma\frac{N-Y}{N})\frac{I}{Y} - (\mu + \alpha + d\frac{I}{N})\right) \\
&= Q\left(\frac{dY}{dt}\frac{1}{Y} + b_0 - \mu - 2b_0N\right) \quad (\mathcal{R}_0 > 1 \text{ implies } \sigma > \text{d})
\end{aligned}$$

If $Q(t) = \frac{Y(t)}{I(t)}|x_2(t)|,$

$$\begin{aligned}
D_+Q(t) &= |x_2(t)|\frac{\frac{dY}{dt}I - \frac{dI}{dt}Y}{I^2} + \frac{Y(t)}{I(t)}D_+|x_2(t)| \\
&= |x_2(t)|\left(\frac{dY}{dt}\frac{1}{Y} - \frac{dI}{dt}\frac{1}{I}\right)\frac{Y}{I} + \frac{Y}{I}\left(k|x_1(t)|\frac{Y}{I} + (b_0 - \mu - 2b_0N - (\mu + d + \rho + k))|x_2(t)|\right) \\
&= \frac{Y}{I}|x_2(t)|\left(\frac{dY}{dt}\frac{1}{Y} - \frac{I}{dt}\frac{1}{I} + (k\frac{Y}{I} + (b_0 - \mu - 2b_0N - (\mu + d + \rho + k))|x_2(t)|\right) \\
&= Q\left(\frac{dY}{dt}\frac{1}{Y} - k\frac{Y}{I} + k\frac{Y}{I} + (\mu + d + \rho + k) + b_0 - \mu - 2rN - (\mu + d + \rho + k)\right) \\
&= Q\left(\frac{dY}{dt}\frac{1}{Y} + b_0 - \mu - 2rN\right).
\end{aligned}$$

If $Q(t) = \frac{N(t)}{I(t)}|x_3(t)|,$

$$\begin{aligned}
D_+Q(t) &= |x_3(t)|\frac{\frac{dN}{dt}I - \frac{dI}{dt}N}{I^2} + \frac{N}{I}D_+|x_3(t)| \\
&= |x_3(t)|\frac{N}{I}\left(\frac{dN}{dt} - \frac{dI}{dt}\frac{1}{I}\right) + \frac{N}{I}\left(\sigma\frac{YI}{N^2}|x_2(t)| - (m_\mu + n_\mu + \sigma\frac{I}{N})|x_3(t)|\right) \\
&= Q(t)\left(\frac{dN}{dt} - \frac{dI}{dt}\frac{1}{I} - (m_\mu + n_\mu)\right).
\end{aligned}$$

Hence, in every case

$$D_+Q(t) \leq H(t)Q(t),$$

where

$$H(t) = max\left\{\frac{dY}{dt}\frac{1}{Y} + b_0 - \mu - 2b_0N, \frac{dN}{dt} - \frac{dI}{dt}\frac{1}{I} - (m_\mu + n_\mu)\right\}.$$

Hence

$$Q(t) \le Q(t_0) e^{\int_{t_0}^{t} H(s)ds}. \tag{34}$$

Let τ be the period of $N(t)$, $Y(t)$ and $I(t)$. Then for any integer n

$$\int_{t_0}^{t_0+n\tau} \frac{dN}{ds}\frac{1}{N}ds = \int_{t_0}^{t_0+n\tau} \frac{dY}{ds}\frac{1}{Y}ds = \int_{t_0}^{t_0+n\tau} \frac{dI}{ds}\frac{1}{I}ds = 0.$$

This follows that

$$\begin{aligned}
&\int_{t_0}^{t} H(s)ds = \int_{t_0}^{t_0+n\tau} H(s)ds + \int_{t_0+n\tau}^{t} H(s)ds \quad \left(n = \left[\frac{t-t_0}{\tau}\right]\right) \\
&\le max\left\{\int_{t_0}^{t_0+n\tau} (\frac{dY}{ds}\frac{1}{Y} + b_0 - \mu - 2b_0 N)ds, \int_{t_0}^{t_0+n\tau} (\frac{dN}{ds} - \frac{dI}{ds}\frac{1}{I} - (m_\mu + n_\mu))ds\right\} + \epsilon \\
&\left(\int_{t_0+n\tau}^{t} H(s)ds < \epsilon \quad \text{for some } \epsilon > 0, \text{ because } H(t) \text{ is bounded }\right) \\
&= max\left\{\int_{t_0}^{t_0+n\tau} (b_0 - \mu - 2b_0 N)ds, -(m_\mu + n_\mu)n\tau\right\} + \epsilon \\
&\le -\gamma_0 n\tau. \quad (\text{ for some } \gamma_0 > 0)
\end{aligned}$$

The last inequality is derived from Lemma ??. It follows from (??) that $\lim_{t\to\infty} Q(t) = 0$. This establishes Lemma ??. □

Remark. From Lemma ?? and Lemma ??, Theorem ?? follows using the strong *Poincaré-Bendixson Theorem* (see, for example, Smith, 1995).

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